

REMARKS

Claims 1-13 were presented at the time of filing. In response to a restriction dated September 18, 2007, claims 1-9 were elected. Claims 3, 5 and 8-13 are cancelled above. Claims 1, 2, 4, 6, and 7 are pending in the application.

Claim 1, as amended above, recites a method for confirming a diagnosis of sepsis in a patient in whom sepsis-associated symptoms are present by determining the level of anti-AGM1 autoantibodies wherein an elevated level when compared to healthy individuals confirms a diagnosis of sepsis. The claimed method is based on Applicants' novel observation that anti-AGM1 autoantibodies are elevated in the blood of known sepsis patients.

Rejection Under 35 U.S.C. §112, second paragraph

Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are amended above to include essential steps and to remove confusing language as detailed in the Office Action.

Withdrawal of the rejection under 35 U.S.C. §112, second paragraph is respectfully requested.

Rejection Under 35 U.S.C. §112, first paragraph

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to satisfy the enablement and written description requirements. As amended, claim 1 is directed to a method for confirming a diagnosis of sepsis in a patient in whom sepsis-associated symptoms are present by determining the levels of anti-AGM1 antibodies in blood from a patient in whom sepsis is

suspected (by virtue of sepsis-associated symptoms), wherein elevated levels when compared to healthy individuals is indicative of sepsis.

Written Description

Claim 1 is amended above to focus the claim on a method for confirming the diagnosis of sepsis. Withdrawal of the rejection under 35 U.S.C. § 112, first paragraph for lack of written description is respectfully requested.

Enablement

An application satisfies the enablement requirement if one skilled in the art, after reading the disclosure, could practice the invention claimed without undue experimentation *In re Wands*, 858 F.2d 731. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation “must not be unduly extensive.” *Chiron Corporation v. Genentech, Inc.*, 363 F.3d 1247. Only after it has been determined that additional experimentation is required, does an analysis under the Wands factors, of whether that experimentation is undue, become applicable.

Preliminarily, a patent disclosure need not enable information within the knowledge of an ordinary artisan. In the instant case, all of the methodology required for the detection of the anti-AGM1 antibodies is well known to those of skill in the biochemical art. Thus, in order to enable the claimed method, all Applicants are required to provide is a correlation between a disease state in a significant number of subjects and the presence of a reliable biomarker in a biological sample from those subjects, regardless of any structural/functional characteristics of the biomarker. Applicants have met that burden.

Independent claim 1 is amended above and is focused on a method for confirming the diagnosis of sepsis in a patient in whom sepsis is suspected as the result of some clinical evaluation, comprising testing blood from the patient for the presence of anti-AGM1 antibodies, wherein an elevated level of antibodies in comparison to healthy individuals is indicative of the presence of sepsis. Applicants respectfully submit that the claims, as amended, are enabled by the disclosure in the specification that the presence of anti-AGM1 antibodies correlates positively

with sepsis.

Clearly, no additional guidance is necessary and no undue experimentation is required for one of skill to practice the claimed method.

Withdrawal of the rejection under 35 U.S.C. §112, first paragraph is respectfully requested.

Rejection Under 35 U.S.C. §103

Claims 1-5 are rejected under 35 U.S.C. §103(a) as being unpatentable over Wirguin et al in view of Weller et al. and Kielian et al.

According to the Office Action, Wirguin et al. teaches determining the presence of anti-GM1 and anti-asialo-GM1 antibodies in serum from patients using ELISA read by a Biotek EIA reader after prior in vivo stimulation of antibody production. Wirguin et al. also allegedly teaches that anti-asialo GM1 and anti-GM1 antibodies cross react with LPS. The Office Action goes on to cite Kielian et al. for its teaching that lipopolysaccharide (LPS) is a constituent of the outer cell wall of gram-negative bacteria and is responsible for the overwhelming immune response in the host during sepsis in order to establish a causal relationship between sepsis and anti-asialo-GM1 antibodies. Lastly, the Office Action maintains that Weller et al. teaches that anti-ganglioside antibodies (including anti-GM1) can be used to diagnose inflammatory diseases in a clinical setting by drawing conclusions based on the presence/absence of antibody. The examiner concludes that, based on the teachings of these references, it would have been obvious to one of ordinary skill in the art to determine the presence of anti-GM1 antibodies in samples from suspected sepsis patients. Applicants respectfully disagree.

The usefulness of any biomarker as an indicator of a disease is predicated on its reliable detection in a particular patient cohort, at levels not seen in healthy individuals. In the present case, Applicants' observation that the levels of anti-AGM1 autoantibodies are consistently higher in sepsis patients than in normal individual gives rise to a correlation not previous known between the presence of anti-AGM1 autoantibodies and sepsis. Applicants are not attempting to

establish a causal relationship between anti-AGM1 autoantibodies and sepsis and a one is not required for patentability. As a preliminary matter, the cited references do not relate to sepsis.

The Office Action attempts to piece together information from several references to explain why one of skill in the art would have been motivated to use anti-AGM1 autoantibodies to diagnose or confirm a diagnosis of sepsis. Applicants respectfully submit that one of skill in the art would not reach that conclusion based on the teachings of the cited references and that the correlation between anti-AGM1 autoantibodies and sepsis was unknown prior to Applicants' observation.

Wirguin et al.

According to the Office Action, "Wirguin et al. teaches determining the presence of anti-GM1 and anti-sialo-GM1 antibodies in serum from patients using ELISA read by a Bioteck EIA reader after prior in vivo stimulation of antibody production... Wirguin et al. also teaches that anti-asialoGM1 and anti-GM1 antibodies cross react with LPS (a component of gram-negative bacteria)."

Wirguin et al. teaches that anti-ganglioside antibodies contained in the sera of 6 patients with chronic motor neuropathy cross-react with the LPS from *some* strains of *Campylobacter jejuni* (CJ), including one that is frequently associated with Guillain-Barre syndrome (GBS) in Japan. Although Wirguin et al. states that "it is not known whether anti-GM1 antibodies in acute or chronic neuropathies are pathogenic, or whether they are only an associated abnormality (page 701, last paragraph), Wirguin et al. suggests that the cross-reactivity between CJ LPS and gangliosides may explain the occurrence of anti-ganglioside antibodies following CJ infection.

Wirguin et al. provides no evidence from which one of skill would conclude that LPS from other bacteria also cross-reacts with GM1 and asialo-GM1 or from which the skilled artisan would expect that there would be elevated levels of these antibodies in a patient with sepsis. Furthermore, Wirguin et al. does not address those situations where the sepsis is elicited by a pathogenic organism other than gram-negative bacteria.

Weller et al.

The Office Action states that “Weller et al. teaches that anti-ganglioside antibodies (including anti-GM1) can be used to diagnose inflammatory diseases in a clinical setting by drawing conclusions based on the presence and/or amount of antibody.” Weller et al., reports on the investigation into the usefulness of gangliosides in the diagnosis of neurological disorders, not sepsis. Weller et al. analyzed sera of 210 patients with various neurological disorders such as amyotrophic lateral sclerosis, lower motor neuron syndromes, acute Guillain-Barre syndrome, multiple sclerosis and Alzheimer’s disease and systemic immunological disorders such as systemic lupus erythematosus or Behcet’s disease (page 455, column 1, first paragraph under Introduction) for elevated levels of antibodies to seven gangliosides. Of the 210 tested, only 32% of patients had at least one “pathological” antibody titre to one of the gangliosides tested; IgG antibodies to GM1 (12%) and GD1b (16%) were the most commonly detected elevated titres (page 456, first paragraph under results). Far from establishing a correlation between neurological disease or immune dysfunction with anti-ganglioside antibody titres, however, Weller et al. observes that “When the distribution of pathological titres was considered, no specific pattern of any diagnostic group emerged.” Weller et al. states that “...an isolated positive gaglioside anti-body titre is a finding of almost no value concerning differential diagnosis. No disease-specific patterns of ganglioside antibodies can be extrapolated from our data.” Weller et al. ultimately concludes that “...the introduction of ganglioside antibody determination as a differential diagnostic test in clinical neurology is only helpful in a few patients with typical lower motor neuron syndromes.” (abstract, page 458, col. 2, last paragraph).

In as much as the teachings of Weller et al. teach away from the use of anti-ganglioside antibodies as markers for diagnosis of neurological disorders and contains no information or evidence with respect to the use of anti-GM1 antibodies as a biomarker for sepsis, the teachings of Weller et al. are not properly combined with the teachings of the other references.

Kielian et al.

Kielian et al. is cited for its teaching that LPS is a constituent of the outer cell wall of gram-negative bacteria and is responsible for the overwhelming immune response in the host during sepsis. Kielian et al., however, also teaches that LPS elicits a broad, *non-specific* cascade of events in vivo, resulting in secretion of a variety of potent mediators and cytokines produced primarily by activated macrophages and monocytes. Kielian et al. goes on to say that the overproduction of these effector molecules, such as interleukin-1 and tumor necrosis factor, contributes to the pathophysiology of endotoxic shock. Kielian et al. does not teach or fairly suggest that the response includes generation of antibodies to LPS, let alone antibodies to LPS that might exhibit some reactivity with gangliosides. Additionally, Kielian et al. teaches that less than half of septic cases originate from Gram-negative infections (page 187, second column), therefore, where sepsis is triggered by a gram-positive, fungal or other infection, LPS would not explain for the presence of elevated levels of anti-AGM1 antibodies.

Thus, it is unlikely that one of skill in the art would conclude from the teachings of the cited references, either individually or in combination, that elevated levels of anti-AGM1 antibodies would be indicative of sepsis.

Withdrawal of the rejection under 35 U.S.C. §103 is respectfully requested.

The Examiner is invited to contact Applicant's Attorney at the telephone number given below if any further questions arise in connection with this Application.

Respectfully submitted,

A handwritten signature in cursive script that reads "Kathy Smith Dias". The signature is written in black ink and is positioned above a horizontal line.

Kathy Smith Dias
Attorney for Applicants
Registration No. 41,707

Dated: July 29, 2008

Please send correspondence to:
Kathy Smith Dias, Esq.
HESLIN ROTHENBERG FARLEY & MESITI P.C.
5 Columbia Circle
Albany, New York 12203-5160
Telephone: (518) 452-5600
Facsimile: (518) 452-5579